

Clues To Autism, Epilepsy, Mental Retardation From Rare Genetic Disorder

24 Sep 2008

A rare genetic disorder called tuberous sclerosis complex (TSC) is yielding insight into a possible cause of some neurodevelopmental disorders: structural abnormalities in neurons, or brain cells. Researchers in the F.M. Kirby Neurobiology Center at Children's Hospital Boston, led by Mustafa Sahin, MD, PhD, and Xi He, PhD, also found that normal neuronal structure can potentially be restored.

If this could be done safely in humans, it might be possible to ameliorate the symptoms of epilepsy, mental retardation and autism, which are frequent complications of TSC, say the researchers. Their findings, accompanied by commentary, were the cover article of the September 15 issue of *Genes & Development*.

TSC causes benign tumor-like lesions, which can affect every organ in the body and are called tubers when they occur in the brain. In the study, Sahin, He, lead author Yong-Jin Choi, PhD, and colleagues show in mice that when the two genes linked to the disease, TSC1 and TSC2, are inactivated, neurons grow too many axons (the long nerve fibers that transmit signals). Normal neurons grow just one axon and multiple dendrites (short projections that receive input from other neurons). This specification of axons and dendrites, known as polarity, is crucial for proper information flow.

"We think if initial polarity is not formed properly, the result will be abnormal connectivity in the brain," says Sahin, who also directs the clinical Multi-Disciplinary Tuberous Sclerosis program at Children's.

Since autism occurs in about half of people with TSC, the findings support the idea that such miswiring causes or contributes to autism, Sahin adds. He has received funding from Autism Speaks, the Manton Foundation and the Tuberous Sclerosis Alliance to pursue this idea further.

"People have started to look at autism as a developmental disconnection syndrome - there are either too many connections or too few connections between different parts of the brain," Sahin says. "In mouse models of TSC, we're seeing an exuberance of connections."

In laboratory experiments, the researchers were able to limit multiple axon formation by using the cancer drug rapamycin to suppress production of a protein called SAD-A kinase. This protein is produced in excess when the TSC1 and TSC2 genes are inactivated, and is found in abundance in the abnormally large cells that make up tubers.

Because increased SAD-A is associated with increased axon growth, the researchers also speculate that the TSC pathway could be manipulated to regenerate or repair axons lost or damaged in spinal cord or other nerve injuries.

"These findings provide a potential explanation for neurological abnormalities in TSC patients and perhaps in people without TSC," says He. "The challenge remains as to how to treat these conditions. We have some clues but a lot more research needs to be done."

Article adapted by Medical News Today from original press release.

The study was funded by grants from the Tuberous Sclerosis Alliance, the Manton Foundation, the Hearst Fund and the National Institutes of Health.